Pre-submission

Cost of Disease Modifying Therapies for Multiple Sclerosis: Is Front-Loading the Answer?

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Abstract

There are now over a dozen disease modifying therapies (DMTs) available to treat multiple sclerosis (MS). They vary in efficacy and safety as well as in cost.

The literature on the cost effectiveness of these is often confusing and contradictory. There is a lack of quality evidence enabling the comparison of different DMTs. There are scarce randomised controlled trials which look at one DMT compared with another that is not IFN or GA. There is also a lack of systematic reviews comparing the efficacy and safety of different DMTs. This makes it difficult to perform good quality cost-effectiveness analyses (CEAs). Furthermore, CEAs in and of themselves are difficult to interpret or compare due to the variation in methods and cost estimations as well as the use of outcome measures which cannot be proven over a reasonable timeframe.

This review looks at the different DMTs available for MS and attempts to draw some conclusions on their cost-effectiveness. It also considers the costs and benefits of front loading the cost of treatment for MS by using more expensive and effective treatment earlier on.

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic autoimmune inflammatory condition of the central nervous system (CNS). It is a pathophysiological process of inflammation, demyelination and neurodegeneration (1). It can cause severe disability as function of the CNS deteriorates (1). Until the 1990s, treatment for MS consisted only of symptomatic control, usually a short course of high dose steroids during exacerbations of the disease (2). MS attacks would lead to progressively worsening disability and early death (3). Since then, a multitude of disease modifying therapies (DMTs) have been developed that can slow the course of the disease. These drugs (Table 1) are high-cost and not without their own risks, but are now widely used to treat relapsing-remitting forms of MS (RRMS).

Diagnosis and Clinical Course

MS is diagnosed when clinical features and investigations indicate there is focal demyelination occurring in more than one location and on more than one occasion, such that there is dissemination in space and dissemination in time (4). Diagnosis of MS often requires the exclusion of other possible diagnoses as presentation is varied (5). Clinical features of MS are many and include motor, sensory and autonomic disturbances (1). Most commonly, MS presents with an acute attack of demyelination resulting in neurological dysfunction (1). In 80% of cases, this will resolve before subsequent attacks occur (1). This is the relapsing-remitting course of the disease. Over time, recovery between episodes diminishes and symptoms become progressively worse without recovery and this is termed secondary progressive MS (SPMS). About 15-20% of people with MS will have a progressive course from onset, known as primary progressive MS (PPMS) (1).

Pathogenesis

There are several proposed mechanisms by which CNS autoimmunity may be initiated in MS. Molecular mimicry may initiate the process by which autoreactive T cells are stimulated by autoantigens (6). By another proposed mechanism, antigens, such as glial or neural proteins may drain into cervical lymph nodes via the glymphatic drainage system (7, 8). Once in the cervical lymph nodes, these antigens are presented to autoreactive T cells by antigen presenting cells (APCs) (6). There seems to be a failure of regulatory T cells to suppress autoreactive T cells upon activation by an autoantigen (9). These autoreactive T cells are able to extravasate into the CNS and they are then re-activated locally, causing the release of cytokines which promote recruitment of microglia and directly cause damage to myelin and axons (10). Autoreactive T cells will also activate B cells and a humoral response will further add to inflammatory cell recruitment and contribute to damage to myelin and axons (11). Alternatively, it may be that memory B cells are the major driving force behind the inflammatory phase in MS and present antigens to T cells or directly damage the CNS via toxic molecules or stimulate the innate immune response (12, 13). Nearly all DMTs seem to deplete memory B cells, and the degree of depletion can be correlated to the efficacy of the drug (12, 13).

Impact

MS carries a huge burden for those afflicted with the disease and those close to them. People with MS experience a decreased quality of life, and life in the most severe stages of MS can be considered to be worse than death (14, 15). Not only do people with MS suffer from physical disability, cognitive impairment can also occur from the earliest stages of the disease onwards (16). People with MS are

more likely to suffer from anxiety and depression than the general population, and they are also more likely to commit suicide (17, 18). Furthermore, people with MS are 40% more likely to get a divorce compared to matched controls that did not have MS (19).

MS has an effect on the ability of people to work full-time and in most cases eventually leads to unemployment. A cost-of-illness study carried out in 2017 looking at data from 16,808 people with MS across 16 European countries found that overall average unemployment was 68% (20).

Relapses can be disabling for people with MS and costly for healthcare systems. In the 2017 European study, 13% of people had experienced a relapse and 7.5% had been admitted to hospital as an inpatient in the last 3 months (20). Overall, 57% of people were using DMTs, with usage varying by country from 26-79% (20).

The 2017 study found that in the UK the total annual cost to society ranged from £11,400 (€12,800) for mild disease (EDSS 0-3) to £22,700 (€25,400) for the moderate disease group (EDSS 4-6.5) and £36,500 (€40,900) for the severe disease group (EDSS 7-9) (21). Overall, the average cost by disease severity across Europe was €22,800, €37,100 and €57,500 for mild, moderate and severe disease (20). For less severe disease, the majority of direct costs were due to health care usage, whereas informal care costs accounted for most of the direct costs in more severe disease (20). Production losses accounted for 39%, 45% and 33% of total costs for mild, moderate and severe disease groups respectively (20).

Table 1: Characteristics of Disease Modifying Therapies for Multiple Sclerosis

DMT	Dose	Pivotal trial efficacy	MoA	Side effects	Monitoring	Annual Cost (UK)*	First year Cost (US) (Year 1 WAC)	EMA Licensing
IFNb-1a (Rebif s.c. injection) (Avonex i.m. injection)	Weekly i.m. injection (30µg) or thrice weekly s.c. injection (20 or 44µg)	s.c.: PRISMS – 27% and 33% reduction in ARR compared to placebo for the 22µg and 44µg dose groups respectively, Increased time to SAD compared to placebo (22) i.m.: 18% reduction in ARR compared to placebo, 37% reduction in SAD vs placebo (23)	The are several proposed mechanisms of action for beta-interferons, including inhibition of immune cell proliferation, inhibition of B and T cell activation (24, 25), increasing anti-inflammatory cytokines (26) , increasing apoptosis of autoreactive T cells (27) and limiting T cell-endothelial adhesion (28, 29).	Injection site reactions, hepatic impairment, depression, flu-like symptoms. Rarer side effects include anaemia, thrombocytopenia, lymphopenia and thrombotic microangiopathy (30, 31). There is an association with capillary leak syndrome in undiagnosed monoclonal gammopathy, which is why the Association of British Neurologists recommend that protein electrophoresis should be carried out prior to commencing therapy (32, 33)	FBC, LFT, renal function, blood pressure at baseline and every 3-6 months Protein electrophoresis at baseline (33, 34)	Rebif: 20/44µg £9,088 /£12,068 Avonex: £9,061	Rebif: $86,416 Avonex: $81,965	RRMS
IFNb-1b (Betaseron or Extavia)	s.c. injection every	34% reduction in ARR compared to placebo, no				Betaseron And Extavia: £7,264	Betaseron: $86,659 Extavia: $72,359	

	other day (250µg)	significant effect on SAD (35)						
Pegylated IFNb-1a (Plegidry)	s.c. injection every two weeks (125µg)	ADVANCE – 35% reduction in ARR and a 39% reduction in 3-month SAD compared to placebo (36)		Flu like symptoms, headache, injection site reactions, raised liver enzymes and depression are common side effects Rarer side effects include hypersensitivity reactions, seizures, injection site reactions, renal damage (37)	Regular monitoring of FBC, LFT, TFT, blood pressure and renal function (37)	£8,500	$81,956	RRMS
Glatiramer Acetate (GA) (Copaxone or Glatopa (generic))	Daily s.c. injection (20mg) Or thrice weekly s.c. injection (40mg)	29% reduction in ARR vs placebo, no significant difference in SAD (38)	GA promotes apoptosis of autoreactive cells by increasing levels of a strongly suppressive subset of regulatory T cells (PD1- Treg cells) (27). Furthermore GA is thought to interfere with antigen presentation and T cell activation, as well as increasing anti-inflammatory cytokines (39, 40).	Injection site reactions, Symptoms mimicking cardiac ischaemia – chest tightness, shortness of breath, palpitations, anxiety (31)	No additional monitoring required	£6,700	20mg: $86,554 40mg: $76,024 20mg Glatopa (generic): $63,193	RRMS
Fingolimod (Gilenya)	Daily oral tablet (0.5mg)	FREEDOMS II – 48% reduction in ARR compared to placebo, no significant reduction in SAD (41) TRANSFORMS – 52% reduction in ARR compared to i.m. IFNb1a, no significant difference in SAD (42)	Fingolimod is a sphingoside-1-phosphate (S1P) receptor antagonist. S1P receptors are expressed in a variety of cells including lymphocytes, neurons and astroglia. Binding of S1P to S1P receptors mediates lymphocyte migration out of lymph glands, and this process is disrupted by fingolimod as it is an S1P analogue. This mainly affects central memory T cells and naïve T cells as these are more likely to re-circulate through lymph glands (43).	First dose bradycardia, First and second degree atrioventricular block, Macular oedema, Lymphopenia, Infections, Elevated liver enzymes, Hypertension (34, 41) Rarely PML (44)	MRI, ECG, VZV IgG serology, pregnancy test, ophthalmology testing, FBC, LFT and blood pressure at baseline Regular 3-monhtly FBC, LFT and ophthalmology during therapy (34, 44, 45)	£19,169	$82,043	2nd line in HARRMS, or 1st line in RESMS
Teriflunomide (Aubagio)	Daily oral tablet (14mg)	TOWER – 36.3% reduction in ARR compared to placebo, reduced risk of SAD by 31.5% (46) TEMSO – Reduced ARR by 31.5% compared to placebo, Reduced risk of SAD by 29.8% (47) TENERE – No difference in ARR compared to s.c. IFNb1a (48)	Teriflunomide is thought to inhibit proliferation of activated T cells by inhibiting pyrimidine synthesis by the enzyme DHODH (dihydroorotate dehydrogenase) (49).	Elevated liver enzymes, Hair thinning, Nausea, Diarrhoea, Hypertension, Peripheral neuropathy (34, 46)	Baseline FBC, LFT, pregnancy test, TB, blood pressure First 6 months of therapy: monthly FBC, LFT After 6 months: FBC and LFT every 6 months (34)	£13,529.	$76,612	RRMS
Dimethyl fumarate (Tecfidera)	120 mg twice daily oral	DEFINE –	Dimethyl fumarate has anti-inflammatory effects, by affecting	Nausea, Diarrhoea, Flushing (59),	Baseline FBC and LFT (34)	£17,898	$82,977	RRMS

	tablet; increased to 240 mg twice daily after 7 days	53% reduction in ARR compared to placebo, 38% reduction in risk of SAD (50) CONFIRM – 44% reduction in ARR compared to placebo, Significant reduction in ARR compared to GA, No reduction in SAD (51)	cytokine release and immune cell differentiation (52-56). It may also have neuroprotective antioxidant effects via Nrf2 (nuclear (erythroid-derived 2) related factor) pathways. In vitro studies showed that dimethyl fumarate protected neurones and glial cells against oxidative stress (57), and that this effect was lost in Nrf2 deficient cells (58). In vivo studies in EAE mice showed raised levels of Nrf2 and improved neuronal survival which was not seen in Nrf2 deficient mice (57).	Rarely PML (60)	Baseline MRI (60) Monitoring of white cell count is necessary as cases of PML have been reported in association with lymphopenia (61, 62)			
Natalizumab (Tysabri)	300mg i.v. infusion every 4 weeks.	AFFIRM – 68% reduction in ARR compared to placebo, and a 42% reduction in risk of SAD (63)	Natalizumab is a monoclonal antibody directed against α4β1 integrin, an adhesion molecule involved in the extravasation of leukocytes across the BBB.	Mild infusion associated symptoms – headache and fever, Hypersensitivity reaction requiring discontinuation of infusion (34), Cases of hepatic injury have been reported (37) The risk of PML after two years of therapy is 1 in 100 in JCV seropositive patients who have received prior immunosuppressive treatment (64), Neutralising antibodies causing delayed hypersensitivity and reduced efficacy (65)	MRI at baseline, then every 3-12 months during therapy based on risk followed by one 3-6 months post-therapy (66) JCV serology every 6 months(66) Consider anti-natalizumab antibody testing after 6 months (65)	£14,730 annually	$78,214	2nd line for HARRMS or 1st line for RESMS
Alemtuzumab (Lemtrada)	First annual course is 60mg via i.v. infusion over 5 days. Second annual course is 36mg via i.v. infusion over 3 days.	CARE MS I – (Alemtuzumab as 1st line therapy) 54.9% reduction in ARR and a 30% reduction in risk of SAD compared to 44µg s.c. IFNb1a (67) CARE MS II – (Alemtuzumab as 2nd line therapy) 49.4% reduction in ARR and a 42% reduction in risk of SAD compared with 44µg s.c. IFNb1a (68)	Alemtuzumab is a mAb targeting CD52, a surface marker on lymphocytes and monocytes. Alemtuzumab treatment depletes lymphocytes and monocytes which subsequently replete over a period of time, at different rates – CD4+ T cells take more than 5 years to reach pre-treatment levels (69). B cells replete over three months and then rise beyond pre-treatment levels, and this is thought to contribute to the secondary autoimmune complications which frequently follow alemtuzumab therapy (69, 70).	Infusion related reactions (90%) - may warrant pre-treatment with steroid, antihistamine and paracetamol (71), Infections, Secondary autoimmune conditions develop in up to 50% of patients after 2 years of therapy (70), Neutralizing antibodies occur in up to 80% of cases after second annual course (68)	Monthly blood tests including FBC, TFT, LFT Consider testing for neutralizing antibodies (71)	£56,360 for full two year course	$103,749	Active RRMS

Ocrelizumab (Ocrevus)	600mg i.v. infusion every 6 months	OPERA I and II– 46% -47% reduction in ARR and 40% reduction in risk of SAD compared to IFNb (72) ORATORIO – 24% and 25% reduction in risk of SAD at 12 and 24 weeks respectively compared to placebo (73)	Ocrelizumab targets CD20, a B cell progenitor antigen, and thereby depletes B cells (12)	Infusion-related reactions, Infections (72)	FBC (74)	£19,160 (£4790 per 300mg)	$65,000	RRMS PPMS
Cladribine (Mavenclad)	1 or 2 10mg oral tablet once per day for four or five days of 2 treatment weeks each year for a total dose of 3.5mg/kg over 2 years	CLARITY – 57.6% and 54.5% reduction in ARR compared to placebo for the 3.5mg/kg and the 5.25mg/kg groups respectively. 33% and 31% reduction in risk of SAD for the 3.5mg/kg and 5.25mg/kg groups respectively compared to placebo (75)	Cladribine is an analogue of deoxyadenosine, which is metabolised to an active compound which causes cell death by incorporating into DNA and inhibiting DNA repair. It rapidly depletes T and B cells (76)	lymphopenia, infections – notably herpes zoster infections (77)	FBC Screen for HIV, TB and Hepatitis before commencing treatment (78)	£2,047.24 per 10mg tablet: Total cost of £50,157 for the 2 year course for a 70kg person	N/A	HARRMS

WAC = wholesale acquisition cost; s.c. = subcutaneous; i.m. = intramuscular; i.v. = intravenous; FBC = full blood count; LFT = liver function tests; TFT = thyroid function tests; PML = progressive multifocal leukoencephalopathy; JCV = John Cunningham virus; VZV = varicella zoster virus; TB = tuberculosis; RRMS = relapsing-remitting multiple sclerosis; HARRMS = highly active relapsing remitting multiple sclerosis; RESMS = rapidly evolving severe multiple sclerosis; ARR = Annualised Relapse Rate, Relapses are usually defined as worsening of neurological signs and symptoms lasting at least 24 or 48 hours, not associated with fever or infection, on a background of at least 30 days clinical stability; EDSS = (Kurtzke) Expanded Disability Status Scale; SAD = Sustained Accumulation of Disability, usually defined as 1 or more point increase in EDSS sustained for at least 3 or 6 months, or 0.5 point increase if baseline EDSS is over 5.5.
*= These are list prices, actual prices may be lower

First-line Injectable Therapies

These were the first DMTs developed for MS, and are still the most commonly used. They are favoured as they have a good safety profile (see Table 1) and have been in clinical use the longest. However, they are less effective than most newer DMTs (Table 1) (22, 23, 35, 38). Of course, there are issues in simply comparing outcome figures across different trials – with varying methods, patient characteristics, outcome definitions, trial lengths performed, safety profiles and trials performed at different times over recent history. A recent meta-analysis showed that although IFN and GA were generally among the least effective DMTs when looking at Annualised Relapse Rate (ARR) and 3-month Sustained Accumulation of Disability (SAD), IFNb1b came out as the most effective in reducing the risk of 6-month SAD, and pegylated IFNb1a was third on the list for reducing 6-month SAD (79). Still, cost-effectiveness models consistently show fewer QALYs gained with IFN and GA compared to other DMTs, even though these models generally take into account both ARR and SAD (80-82).

These drugs were initially deemed by the National Institute for Clinical Excellence (NICE), within the UK, to not meet their cost-benefit threshold, but were provided by the NHS under the risk-sharing scheme (RSS), in which the drug would be approved by NICE for use in the NHS if it was found to be cost-effective in a 20-year model based off of 10 years of follow-up data, and if not the price of the drugs for these patients would be discounted by the manufacturer (83). The outcome of the re-evaluation by NICE in early 2018 further concluded glatarimer acetate and all the beta interferons

except Betaferon are recommended for use in people with RRMS but only if provided with a discount under commercial agreement with suppliers (84). Betaferon was not considered to be cost-effective (84).

Oral Therapies

Current oral therapies for MS include teriflunomide, fingolimod, dimethyl fumarate and oral cladribine prodrug (Table 1). Although these oral therapies have the advantage of not being injected, they do still require regular blood test monitoring. In terms of effectiveness, Teriflunomide is as effective as IFN and GA, whilst dimethyl fumarate and fingolimod are more effective (79). However, these are still not as effective as the second-line injectable therapies natalizumab and alemtuzumab (79). The annual cost of these drugs varies from £13,500-£25,000, making them relatively expensive compared to IFN and GA. Oral cladribine is arguably the most effective of the oral agents for MS (77). In a recent cost effective analysis (CEA), cladribine was found to be more cost-effective than alemtuzumab and natalizumab (85). This may in part account for the relatively rapid approval of oral cladribine by NICE and availability to the NHS shortly following approval by the European Medicines agency. In terms of safety, these oral DMTs are all relatively safe compared to DMTs such as natalizumab and alemtuzumab (see Table 1).

Second-line Therapies

Natalizumab was the first monoclonal antibody licensed for use in MS. It is one of the most effective therapies available (79). At £14,730 annually, it is one of the less expensive DMTs for MS. However, this is not taking into account the cost for any additional monitoring required. Indeed, for one CEA the price per QALY gained went from 38,000 EUR (£32,000) when looking only at direct healthcare costs, to 59,000 EUR (£50,000) when taking into account the extra monitoring required due to the risk of progressive multifocal leukoencephalopathy (PML) (80).

PML is a progressive inflammatory condition in the brain caused by the John Cunningham virus (JCV). It can be associated with immunosuppression and a low white cell count (86). Currently, the only treatment is to terminate immunosuppressive therapy in order to minimise disease progression. It has a high mortality rate, approximately 20-25% at 6 months (87, 88). This is a rare occurrence with fingolimod and dimethyl fumarate therapy (44, 89). Though no cases have yet been reported with ocrelizumab therapy (unless following natalizumab therapy (90)), PML has been known to occur with anti-CD20 antibodies (91). The greatest risk of PML reported so far occurs with natalizumab therapy. The risk of PML after two years of therapy is about 1 in 100 in JCV seropositive patients who have received prior immunosuppressive treatment (64). Therefore natalizumab therapy requires MRI monitoring and JC virus serology status is monitored at 6-monthly intervals whilst on therapy (92).

Alemtuzumab is another monoclonal antibody that is currently licensed for RRMS. According to a recent meta-analysis, it is the most effective treatment for RRMS when looking at outcomes such as ARR improvement and preventing disability progression (79). However, due to the fact that disease progression is not always defined by the same criteria in different studies, and people in the pivotal alemtuzumab trials had a shorter disease course and therefore perhaps more neurological reserve to respond to therapy, the evidence for efficacy in preventing disease progression is less reliable (79). Significant monitoring is needed as the risk for secondary autoimmunity is as high as 50% of those treated with two annual courses (70). The cost of these potential complications is high as they include

thyroid autoimmunity, ITP (immune thrombocytopaenic purpura) and renal anti-glomerular basement membrane disease (70). These are costly to manage and can lead to severe disability and death (70). Furthermore, neutralizing antibodies occur in up to 30% of patients following the first course (68). This incidence increases to 80% after the second annual course (68). In many cases neutralizing antibody levels decrease over the year between treatment courses, rendering them non-problematic, but in some cases they persist causing treatments to be ineffective (68). Repeated courses past two years may not be necessary though as effects can last up to 6 years and possibly beyond (93-96).

Two phase III trials were conducted with ocrelizumab for RRMS, and one for PPMS (72, 73). Its efficacy data in these pivotal trials was comparable to current most effective DMTs. SAEs occurred at a similar rate as with IFN treatment or placebo, making it relatively safe compared to most other DMTs (72, 73). However, development of ocrelizumab was halted for rheumatoid arthritis and lupus due to deaths from infection (97, 98). It remains to be seen what the long-term safety profile of this drug will be like. Currently, it is administered every 6 months, however the phase II extension study suggests that like alemtuzumab and oral cladribine, that ocrelizumab may have induction therapy potential with long-term benefit from short courses of therapy (12, 13). Although cost-benefit value of ocrelizumab is accepted, this agent has yet to be seen as sufficiently cost-effective for treatment of PPMS. Although the manufacturers had offered supply to the NHS at a lower price than for use in relapsing MS variants, NICE has yet to entertain this model (99).

Haematopoietic Stem Cell Transplantation

A recent study showed total suppression of CNS inflammatory processes with autologous haematopoietic stem cell transplant (aHSCT), evidenced by a complete lack of relapses in any patients during a 7-year follow up period (100). Disability progression was halted in 70% of patients (100). This is similar to other studies looking at aHSCT for MS, but the total suppression of CNS immunity had not been seen before (101-103). Effects seen have been dramatic, but the procedure is currently reserved for last resort cases due to the high associated risk of mortality at around 5% (104), although this can be minimised in specialist centres to 1-2% (105). If safety improvements can be made and high efficacy results continue to be seen, then the procedure may become more commonplace in the future.

Cost-Effectiveness Analyses

The CEAs for MS drugs use models to predict the long-term cost and benefit of drugs based on published trial data. There are various issues with this. CEAs can take on the societal or the third-party payers perspective. The third party payers perspective includes only the cost of the drug and the cost to healthcare providers, whereas societal perspective will include informal care costs and indirect costs, such as the cost of unemployment. Thus, changing the perspective will impact the cost-effectiveness of the drug. A societal perspective is arguably more useful and realistic, but also less reliable than the payers perspective. Indeed, methods for estimating costs to society can vary widely between CEAs (106).

Changing the length of time of the model can affect the outcome of CEAs (107), as can using different sources for utility values (108). Some models do not account for non-drug care costs or the costs of complications and side effects of treatment. Many CEAs fail to transparently describe and justify their methods of cost estimation and the limitations of their studies, and sponsored CEAs tend to favour

the drug of the sponsor (106, 107). Furthermore, as the payer threshold per QALY is known, health economic data may be adapted to fit this threshold.

A CEA is only as good as the original trial data being used, therefore models using data from longer and larger trials with similar study populations are preferable. Head-to-head comparative randomized controlled trials (RCTs) are ideal but there is a near total dearth of RCTs comparing any DMT with any other DMT other than IFN or GA (79). Yet there are a number of cost-effectiveness models comparing various DMTs with each other, using data from separate trials or from historical comparator populations (106, 109). However comparisons are emerging following comparisons of real life usage using registries such as NARCOMS (North American) and MSBase (110).

The RCTs need to minimise the heterogeneity of outcome measures used. Defining SAD by 3 months instead of 6 may overestimate the rate of disability progression. Similarly, defining a relapse as lasting 24 verses 48 h can impact the results. Furthermore, as treatments become more effective these outcome measures become less relevant. There has been a move towards inclusion of other end points, notably that of the proportion of patients with no evidence of disease activity (NEDA). NEDA has been defined as “absence of new or enlarging T2 lesions or T1 gadolinium-enhancing lesions on MRI and no sustained EDSS score progression or clinical relapse” (111). In light of the improving efficacy of therapies, NEDA has become an important end-point. However, current definitions of NEDA may not pick up slight changes in disability progression (112). Furthermore, none of these outcome measures take into account the impact of MS and treatments on things like mental health, working status and quality of life, all of which may be more pertinent to look at as treatments are becoming more effective at suppressing disease activity as measured by relapses, MRI lesions and EDSS progression. As such NEDA evolves as new outcome measures form part of the definition such as brain atrophy and neurofilament levels (113).

A problem with long-term CEAs is that they cannot be challenged in a reasonable timeframe. There has been a call recently for manufacturers to support claims from CEAs with a protocol for empirical evaluation over a reasonable short-term timeframe, so that decision makers can confirm decisions on whether treatments shall be made available in their healthcare system (114). Long-term CEAs are arguably more useful to estimate the overall cost-benefit of a drug, especially when looking at whether more expensive but effective drugs can be a more cost-effective option in the context of a lifetime. However, these predictions cannot be challenged or tested, and as such cannot provide any real evidence of cost-effectiveness. Using cost per relapse avoided or year of NEDA instead of QALYs gained provides outcomes that can be verified in short-term studies. (83).

For the reasons outlined above, it is difficult to draw any conclusions from CEAs about which DMT is most cost effective.

Front-Loading of Costs

Recently, evidence is pointing towards the fact that front-loading of treatment costs in MS may be more cost-effective than paying for longer-term treatments, which are cheaper. It seems that drugs that are better at depleting memory B cells are more effective, and that induction of depletion may be all that is needed, without sustained treatment (12, 76). Furthermore, there is evidence to suggest that treating earlier in the disease course is more effective (115).

Currently, some of the more expensive and effective DMTs are showing promise as induction therapies with repeated courses after 1-2 years not being necessary, thus lowering the cost per QALY. Some of the best efficacy results have been seen with drugs such as alemtuzumab, ocrelizumab and oral cladribine, and there is evidence for all of these that treatment beyond the first couple of years may not be necessary (72, 93-96, 116). This means that though these are among the most expensive DMTs for MS, the cost over a lifetime may actually be less than some of the cheaper DMTs that require longer periods of treatment (85, 107, 117-119). Furthermore, treating aggressively early on in the disease to achieve NEDA may reduce hospital visits and admissions, further reducing the cost to healthcare systems and society (120). Indeed, one retrospective cohort study looking at the relationship between healthcare costs and disease progression in Italy found that higher care spending was associated with reduced progression over a 14 year time period (121). Long-term benefit from short treatment cycles means that the DMT are only present for short period and therefore may reduce problems of drug-drug interactions with the polypharmacopia of agents that will be needed to deal with symptomatic issues and neurorepair and protection. However, problems with these DMTs include the fact that they are new and long-term safety has not yet been determined. Furthermore, long-term efficacy has not been confirmed beyond a few years.

Conclusion

MS is a progressively disabling disease that has a significant impact on quality of life. This has implications for the individual with MS, for their families and for Society as people with MS are more likely to be unemployed and to require informal care from friends and family. This is in addition to the formal healthcare cost of managing the disease and the disability caused by it. Clearly there is a great need for treatments that can slow the progression of the disease and prevent disability.

Current first-line therapies are relatively safe and cheap but less effective compared to second-line therapies (79). There may be something to be said for using more expensive therapies that are also more effective to reduce the long-term risk of disability and to reduce long-term costs. Currently it is difficult to say what the long term outcomes of different therapies may be as there is not enough long-term follow-up data. Cost-effectiveness models have aimed to compare DMTs with each other over long-term time horizons, but their results are often difficult to interpret or compare across analyses. Currently, the drugs with the most benefit tend to be those that carry the most risk and highest price tag. It may be worth using more aggressive measures earlier on as front-loading the cost means the cost of long-term disability progression is reduced. Further head-to-head RCTs, RCT follow-up studies and CEAs are needed to answer these questions, and these need to take on board the recommendations that have been made for improving their quality. As patents expire notably on chemical small molecules that have low costs, the treatment landscape and cost-effectiveness requirements may change (122).

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